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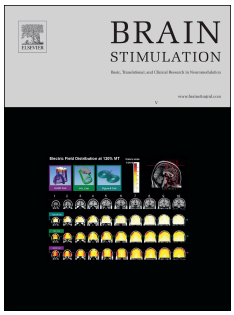

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Brain Stimulation (Original Article)

Non-motor outcomes of subthalamic stimulation in Parkinson's disease depend on location of active contacts

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Veerle Visser-Vandewalle – surgical intervention, critical revision of manuscript

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Glossary: ADL = activities of daily living; **DBS** = deep brain stimulation; **df** = degrees of freedom; **HADS** = Hospital Anxiety and Depression Scale; **LEDD** = levodopa equivalent daily dose; **NMS** = Non-motor symptoms; **NMSS** = NMSScale; **NMSQ** = NMSQuestionnaire; **PD** = Parkinson’s disease; **PDQ-8 SI** = 8-item PD Questionnaire Summary Index; **QoL** = quality of life; **SCOPA-A, -B and -C** = Scales for Outcomes in PD-motor examination, -activities of daily living and motor complications; **STN** = subthalamic nucleus

Abstract

Background: Subthalamic nucleus (STN) deep brain stimulation (DBS) improves quality of life (QoL), motor, and non-motor symptoms (NMS) in Parkinson's disease (PD). Few studies have investigated the influence of the location of neurostimulation on NMS.

Objective: To investigate the impact of active contact location on NMS in STN-DBS in PD.

Methods: In this prospective, open-label, multicenter study including 50 PD patients undergoing bilateral STN-DBS, we collected NMSScale (NMSS), NMSQuestionnaire (NMSQ), Hospital Anxiety and Depression Scale (anxiety/depression, HADS-A/-D), PDQuestionnaire-8 (PDQ-8), Scales for Outcomes in PD-motor examination, motor complications, activities of daily living (ADL), and levodopa equivalent daily dose (LEDD) preoperatively and at 6 months follow-up. Changes were analyzed with Wilcoxon signed-rank/t-test and Bonferroni-correction for multiple comparisons. Although the STN was targeted visually, we employed an atlas-based approach to explore the relationship between active contact locations and DBS outcomes. Based on fused MRI/CT-images, we identified Cartesian coordinates of active contacts with patient-specific Mai-atlas standardization. We computed linear mixed-effects models with x-/y-/z-coordinates as independent, hemispheres as within-subject, and test change scores as dependent variables.

Results: NMSS, NMSQ, PDQ-8, motor examination, complications, and LEDD significantly improved at follow-up. Linear mixed-effect models showed that NMS and QoL improvement significantly depended on more medial (HADS-D, NMSS), anterior (HADS-D, NMSQ, PDQ-8), and ventral (HADS-A/-D, NMSS, PDQ-8) neurostimulation. ADL improved more in posterior, LEDD in lateral neurostimulation locations. No relationship was observed for motor examination and complications scores.

Conclusions: Our study provides evidence that more anterior, medial, and ventral STN-DBS is significantly related to more beneficial non-motor outcomes.

1. Introduction

Subthalamic nucleus (STN) deep brain stimulation (DBS) is an effective treatment option for patients with advanced Parkinson’s disease (PD) improving quality of life (QoL) [1], motor [2], and non-motor symptoms (NMS) [3, 4].

In PD, motor outcomes may depend on the location of active contacts, as previous studies have reported that neurostimulation in the zona incerta [5] or lateral STN border [6] may result in better motor outcome than stimulation of other STN subregions. However, other studies have challenged these observations and reported no significant differences of motor examination outcomes for different active contact sites within the STN and subthalamic region [7-10]. Regarding NMS, previous studies have focused on neuropsychological [11, 12] and neuropsychiatric [7, 9] outcomes leading to the suggestion that focusing DBS to the dorsolateral STN may be beneficial for these outcomes [9, 12]. However, the relationship of active contact locations with non-neuropsychological, non–neuropsychiatric NMS and other important outcomes, such as QoL and activities of daily living (ADL), has not been systematically studied yet.

Therefore, we investigated a wide range of NMS and hypothesized that non-motor outcomes of STN-DBS in patients with PD depend on the location of active contacts. Furthermore, we explored the relationship with motor manifestations and QoL.

2. Materials and methods

2.1. Design and Ethical approval

We prospectively recruited patients in an international, multicenter, open-label study (DBS arm of the NILS study which also incorporated the EuroInf study; German Clinical Trials Register #6735) [3] and retrospectively analyzed imaging data from three centers

(Cologne/London/Venice). The study was carried out in accordance with the Declaration of Helsinki and authorized by local ethics committees (Cologne, #12–145; United Kingdom: NRES South East London REC3, 10/H0808/141, #10084). All patients gave written informed consent prior to study procedures.

2.2. Participants and surgical procedures

PD diagnosis was based on the British Brain Bank criteria. Patients were screened for DBS treatment as per clinical routine according to published guidelines of the International PD and Movement Disorders Society. Eligibility for DBS required a good levodopa test response (>30% improvement, Unified PD Rating Scale–III).

We included consecutive patients who underwent bilateral STN-DBS (01/2011–12/2014). We excluded patients with clinically relevant cognitive impairment or neuropsychiatric symptoms as assessed in multi-disciplinary teams including expert neuropsychologists and neuropsychiatrists, and patients without postoperative CT-imaging (see Supplemental document).

STN targeting was performed visually on preoperative MRI and supported by intraoperative electrophysiological mapping with micro-/macroelectrode recordings. The final position of stimulation leads was based on the best effects on motor symptoms with the lowest stimulation intensity and largest safety margin. Proper stimulation lead placement was confirmed by postoperative high-resolution CT-imaging (see methods section 2.4.). As per clinical routine, DBS was activated within a few days after surgery with 60 µs and 130 Hz as standard pulse parameters. Voltage and levodopa equivalent daily dose (LEDD) were adjusted according to patients’ requirements.

2.3. Clinical assessment

Clinical assessments were performed at preoperative baseline (MedON) and postoperative follow-up 6 months after surgery (MedON/StimON) using following scales:

1) QoL was surveyed with the 8-item PD Questionaire (PDQ-8) which has previously been employed in patients with PD undergoing DBS [13-15]. PDQ-8 scores are reported as Summary Index (PDQ-8 SI) ranging from 0 (no impairment) to 100 (maximum impairment).
2) NMS were assessed with three scales:
   a) The clinician-rated NMSScale (NMSS) was employed to investigate NMS in nine different domains (cardiovascular, sleep/fatigue, mood/apathy, perceptual problems/hallucinations, attention/memory, gastrointestinal, urinary, sexual function, and miscellaneous symptoms including unexplained pain, smell/taste changes, weight changes, and excessive sweating) over the last four weeks [16]. The NMSS ranges from 0 (no NMS) to 360 (maximum NMS).
   b) The patient-based NMSQuestionnaire (NMSQ) consisting of 30 dichotomized items was collected testing the presence of NMS over the last four weeks [17]. The NMSQ ranges from 0 (no NMS) to 30 (maximum NMS).
   c) Anxiety and depression were evaluated with subscales of the Hospital Anxiety and Depression Scale (HADS-A and -D) which respectively range from 0 (no anxiety/depression) to 21 (maximum anxiety/depression) [18].
3) Motor aspects: Motor examination, ADL, and motor complications were assessed with corresponding parts of the Scales for Outcomes in Parkinson’s disease (SCOPA-A, -B, and -C). The SCOPA score was derived from the Unified PD Rating Scale and the two scales strongly correlate [19]. SCOPA-A, -B, and -C range from 0 (no impairment) to 42, 21, and 12 points respectively (maximum impairment).

4) The therapeutic medical regimen was recorded calculating the LEDD according to the method of Tomlinson et al. [20]. The total electric energy delivered was computed according to the method of Koss et al. [21].

2.4. Image analysis

Stereotactic preoperative MRI and postoperative CT images with spatial resolution of 1.00–1.25 mm were used for image analysis. Images were fused using the Optivise software (Medtronic Inc., Minneapolis/Minnesota/USA).

Locations of ventral and active contacts derived from these images were referenced to the mid-commissural point, the equidistant point on a line between the anterior and posterior commissure. To account for patients’ individual anatomical differences, locations were standardized to the Mai-Atlas as suggested by Videen et al. [22]. This method standardizes midbrain nuclei to atlas space with a mean accuracy <1 mm. Further imaging methods employed in the present study are detailed elsewhere [23, 24]. These imaging methods were chosen as they can be easily accessed and reproduced by most DBS centers.

2.5. Statistical analysis

All statistical analyses were performed using SPSS (v24.0.0.0, SPSS Inc., Chicago/Illinois/USA).

2.5.1 Clinical outcomes at baseline and follow-up

Normal distribution of clinical scores was checked with the Shapiro-Wilk test. Significant changes at follow-up were detected with the Wilcoxon signed-rank or t-test, when parametric criteria were fulfilled, and Bonferroni correction for multiple comparisons. Test change scores

($Test_{baseline}$–$Test_{follow\text{-}up}$) were computed for additional explorative analyses. Effect sizes were calculated [25]. Furthermore, as we were interested in the relationship between NMS and LEDD changes, Spearman correlations between these outcome parameters were computed.

2.5.2 Exploratory linear mixed-effect models

Linear mixed-effect models (SPSS ‘MIXED’ command) were employed to explore a possible dependency of test change scores on active contact locations as this method is appropriate for data in which within-subject effects can be expected.

In the linear mixed-effects models, we entered active contacts’ x-/y-/z-coordinates as independent and respective test change scores as dependent variables. To account for a possible dependency of clinical responses on x-/y-/z-coordinates from two hemispheres per patient, we included the binary parameter ‘hemisphere’ as a within-subject variable. Subsequently, we tested two possible type III Maximum Likelihood models: In ‘models A’ the fixed effects included x-/y-/z-coordinates. In ‘models B’ we additionally included the three-component interaction (x*y*z-coordinates) to explore possible effects in three-dimensional space that could not be detected in ‘models A’. Akaike’s Information criterion was employed to compare the goodness of fit for ‘models A and B’.

2.5.3 Dichotomization into “responders” and “non-responders”

Furthermore, according to a previously published method [3], patients were classified as “responders”, if they experienced a clinically relevant improvement using a designated cohort-specific threshold (>½ SD $test_{baseline}$), and remaining patients were classified as “non-responders”. To confirm results of linear mixed-effect models, we pooled bihemispheric active

contact coordinates and employed paired t-tests to detect significant differences between “responders” and “non-responders”.

3. Results

We screened 88 consecutive patients from our database and included 65 patients with all necessary valid baseline and 6 months follow-up assessments in the analysis. Of these, fourteen patients from Cologne were excluded as postoperative CT imaging was not available because the final position of stimulation leads as per clinical routine was confirmed with intraoperative teleradiography before August 2012 [26]. One patient was excluded due to a clinically relevant lateral deviation of the stimulation lead. The final study sample consisted of 50 patients (31 male) aged 60.9 years (±8.3) at intervention with 10.3 years (±4.4) disease duration and a median Hoehn&Yahr score=2.5 (interquartile range: 2.0–3.0).

3.1. Clinical outcomes at baseline and follow-up

Table 1 illustrates significant improvements of PDQ-8 SI, NMSS total score, NMSQ, SCOPA-A, SCOPA-C and LEDD at follow-up. Trends were observed for SCOPA-B and HADS total score before Bonferroni-correction. HADS-A improved significantly at follow-up (baseline: 5.76 ±3.97; follow-up: 4.36 ±2.81; p=0.009); HADS-D improvement did not reach statistical significance (baseline: 4.98 ±3.24; follow-up: 4.16 ±3.30; p=0.123). Relative reductions for outcome parameters ranged between 20.0% (SCOPA-B) and 51.8% (LEDD). Effect sizes were "small" (0.2-0.49) for HADS and SCOPA-B, "moderate" (0.5-0.79) for PDQ-8 SI, NMSS, NMSQ, and SCOPA-C, and "large" (>0.80) for SCOPA-A and LEDD. Spearman correlations between LEDD changes and HADS, NMSQ, and NMSS total score changes were not significant (p>0.05).

3.2. Cartesian coordinates of ventral and active contacts and stimulation characteristics

Figure 1 illustrates the locations of bilateral stimulation electrodes of all patients. Table 2 shows mean Cartesian coordinates of ventral and active contacts. We detected no significant differences between locations of ventral contacts of left- and right-hemispheric stimulation leads for y-, z-, and for absolute values of x-coordinates (all $p>0.05$, paired t-test).

The mean bihemispheric total electric energy delivered was 159.9 µJoule (±206.8). There was no significant difference between the left- and right-hemispheric total electric energy delivered (left: 96.67 µJoule ±186.5; right: 63.25 µJoule ±54.76; $p>0.05$; see Supplemental document).

3.3. Exploratory linear mixed-effect models

Based on Akaike's information criterion, 'model A' was best suited to predict the majority of outcome parameters (PDQ-8 SI, NMSS, HADS-A and -D, SCOPA-A, -B, and -C). In contrast, 'model B' better predicted NMSQ and LEDD outcomes. However, as the Akaike Information criterion differences between 'model A' and 'model B' were small for both scales (NMSQ: 589.4 and 588.3; LEDD: 1509.2 and 1507.3) and the results of both models did not significantly differ, only 'model A' results are reported.

Table 3 presents linear mixed-effect model results for $Test_{change\ score}$ responses based on Cartesian coordinates. We observed the following significant relationships between locations of active contact and clinical outcomes:

- X-axis: More medial location of active contacts significantly corresponded to more NMSS improvement ($\beta=-5.59$; $F_{(1,92)}=5.02$; $p=0.028$; deegrees of freedom were rounded to the next integer) and HADS-D improvement ($\beta=-0.55$; $F_{(1,87)}=5.06$; $p=0.027$). In

contrast, more lateral active contact sites were associated with more LEDD reduction (β=76.02; $F_{(1,94)}$=5.04; p=0.027).

- Y-axis: More anterior neurostimulation location was significantly related to more improvement of NMSQ (β=0.69; $F_{(1,96)}$=4.45; p=0.037), HADS-D (β=0.61; $F_{(1,90)}$=7.23; p=0.009), and PDQ-8 SI (β=3.40; $F_{(1,94)}$=8.48; p=0.004). In contrast, more posterior active contact sites were associated with more beneficial SCOPA-B response (β=-0.48; $F_{(1,92)}$=4.51; p=0.036).
- Z-axis: More ventral neurostimulation location corresponded to more improvement of NMSS (β=-6.12; $F_{(1,93)}$=5.48; p=0.021), HADS-A (β=-0.55; $F_{(1,90)}$=4.72; p=0.032), HADS-D (β=-0.51; $F_{(1,90)}$=4.10; p=0.046), and PDQ-8 SI (β=-2.51; $F_{(1,93)}$=4.18; p=0.044).

No significant relationship with active contact locations was found for SCOPA-A (hemibody/total scores) and SCOPA-C (all p>0.05). Figure 1 illustrates results of linear mixed-effect models in a three-dimensional model of the Mai-atlas.

To explore effects on specific NMS, we explored linear mixed-effect models of $NMSS\ domain_{change\ score}$ responses based on Cartesian coordinates (see Supplemental table e-1). In these explorative analyses of our data, more ventral active contact location was associated with improvements of NMSS domain 2 (sleep/fatigue; β=-1.36; $F_{(1,94)}$=4.54; p=0.036) and NMSS domain 3 (mood/apathy; β=-2.47; $F_{(1,94)}$=6.68; p=0.011). For the latter, we also observed a significant relationship with more medial neurostimulation sites (β=-2.41; $F_{(1,89)}$=7.12; p=0.009). More anterior active contact location was associated with improvements of NMSS domain 6 (gastrointestinal symptoms; β=1.30; $F_{(1,94)}$=8.76; p=0.004). Linear mixed-effect models (constructed in 'model A' design after testing Akaike Information criterion) showed no significant relationship between total electric energy delivered and in x-/y-/z-coordinates of active contacts (all p>0.05).

3.4. Dichotomization into “responders” and “non-responders”

Based on a cohort-specific method (>½ SD $test_{baseline}$), we defined the following thresholds for a clinically relevant improvement (/maximum score) for a classification into the “responder” group: PDQ-8 SI 8.03 (/100), NMSS total score 17.37 (/360), NMSQ 2.47 (/30), HADS-A 1.98 (/21), HADS-D 1.62 (/21), SCOPA-A 3.0 (/42), SCOPA-B 1.67 (/21), SCOPA-C 1.46 (/12), and LEDD 271 mg. Although all scales improved on the group level (ranging from 20% to approximately 50%; see table 1), only approximately 50% of patients or less were to be classified as “responders” for the NMSS, NMSQ, HADS, PDQ-8 SI, SCOPA-A, -B, and -C.

Confirmatory analyses of neurostimulation locations of “responders” and “non-responders” resulted in the following significant differences:

- X-axis: No significant differences between neurostimulation locations of “responders”/“non-responders” were observed for the x-axis.
- Y-axis: In patients with clinically relevant improvements of NMSQ (“NMSQ responders”), mean active contact locations were 1.13 mm more anterior (“NMSQ responders”: 0.12 mm ±1.75; “NMSQ non-responders”: -1.25 mm ±1.72; $p<0.001$), and in “SCOPA-B responders” 1.10 mm more posterior compared to “SCOPA-B non-responders” (“SCOPA-B responders”: -1.12 mm ±1.76; “SCOPA-B non-responders”: -0.02 mm ±1.84; $p=0.005$).
- Z-axis: In “NMSS responders”, mean locations of neurostimulation were 0.69 mm more ventral than in “NMSS non-responders” (“NMSS responders”: -3.38 mm ±1.40; “NMSS non-responders”: -2.69 mm ±1.86; $p=0.044$).

Figure 2 illustrates clinical outcomes from baseline to follow-up and linear mixed-effect models (see results section 3.3) on a three-dimensional model of the Mai-atlas [23].

4. Discussion

In this prospective, observational, multicenter study including a cohort of 50 patients with PD, bilateral STN-DBS significantly improved QoL, non-motor and motor symptoms.

In line with previous studies, relative reductions indicated considerable improvements of all outcomes on the group level (from 20.0% SCOPA-B improvement to 50.1% LEDD improvement with other outcomes ranging in-between) [1-3, 27]. However, the analysis of individual patients revealed a more complex picture. We observed that the ratio of patients who experienced clinically relevant improvements on respective scales (“responders”) was as low as approximately 33% for HADS total score and approximately 50% for the PDQ-8 SI, NMSQ, NMSS, SCOPA-A, -B, and -C scores.

To better understand DBS-related factors that may contribute to this high inter-individual variance, we explored the relationship between locations of active contacts and clinical outcomes. Active contact locations in our cohort resembled those in a previous study with less than 1 mm difference in mean locations in the x-, y- and z-axis and less than 10° difference in mean AC-PC angle of lead trajectories (present study: see table 2 for active contact locations and figure 1 for lead trajectories of all patients, mean AC-PC angle 52.33° ±11.40 degrees; study by Nestor et al.: mean active contact locations in x-axis 11.82 mm ±1.37, y-axis -1.47 mm ±2.20, and z-axis -2.60 mm ±2.57, and mean AC-PC angle 61.93° ±5.95) [10]. These small differences may result from the visual STN targeting taking patients’ individual anatomy into account.

4.1. Non-motor outcomes and active contact locations

We were particularly interested in non-motor outcomes of DBS because of the emerging concept of non-motor effects of DBS [28]. Evidence of beneficial effects of STN-DBS on NMS was not only reported in studies employing clinician-administered and patient-based scales, e.g. for depression [29], anxiety [30], and pain [31], but also in laboratory-assisted studies

employing methods, such as polysomnography for sleep [32], $^{13}CO_2$ excretion for gastrointestinal [33], urodynamic examinations for urinary [34], or tilt tests for orthostatic symptoms [35].

Several factors could explain the observed dependency of anxiety, depression, sleep, and gastrointestinal symptoms on active contact locations in our cohort:

- Anxiety and depression: Previous studies have reported an improvement of these neuropsychiatric symptoms by bilateral STN-DBS [36] and more beneficial outcome has been reported for more ventral active contact locations [37]. According to the concept of the functionally tripartite STN, the limbic subregion is located in the medial, anterior, and ventral STN and DBS closer to this STN subregion, as observed in our study, may impact upon neuropsychiatric symptoms. A possible mechanism of action is a modulation of the limbic circuitry which includes brain regions relevant to anxiety and depression (amygdala, nucleus accumbens, ventral striatum, mediodorsal thalamic nucleus, and the limbic and paralimbic cortices) [38]. Furthermore, a modulation of the medial forebrain bundle, located in close proximity of the medial STN (less than approximately 5 mm with even closer projections), could result in DBS effects on neuropsychiatric symptoms [39]. While neurostimulation of non-motor STN subregions or the medial forebrain bundle may result in beneficial effects on mood, early case reports have provided evidence for an induction of acute severe depression by substantia nigra stimulation [40, 41].
- Sleep: Our analyses indicated that more ventral neurostimulation locations may be beneficial for sleep outcome. This may result from more spread of current to the pedunculopontine nucleus which is located ventral of the STN within approximately 5 mm with even closer projections [42] and has previously been associated with sleep improvement [43].

- Gastrointestinal symptoms: An improvement of gastric motility by bilateral STN-DBS has previously been reported [33]. Furthermore, studies have provided evidence that gastric motility is associated with an activation of autonomic centers, such as the frontal cortex, cingulate cortex, insula, ventral posterolateral and dorsomedial thalamic nuclei [44] which mainly project to and from non-motor STN subregions that are also located more anterior than the motor STN [38].

4.2. Quality of life and motor outcomes and active contact locations

The fact that PDQ-8 SI improvement was significantly related to more anterior active contact locations may be explained by the fact that NMS scales performed similarly (significant relationship with anterior location of neurostimulation for HADS-D and NMSQ, trend for NMSS). The strong relationship between QoL and NMS is well established and, in fact, there is an overlap for depression items between scales (PDQ-8 item #3 “feeling depressed”, HADS-depression subscale items, NMSQ item #16 “feeling sad”).

Previous studies have provided evidence that motor STN subregions are located in the lateral/posterior/dorsal part [38], which may explain that we observed more ADL improvement in posterior and more LEDD reduction in lateral neurostimulation locations. However, the relationship between motor manifestations and neurostimulation locations seems subtle as, in line with previous studies [7-10], responses for motor examination and complications were not significant. To include axial symptoms and account for ipsilateral corticospinal tract projections, we additionally carried out analyses with motor examination total score improvements. No significant relationship with neurostimulation locations was found for both scores.

4.3. Methodological considerations and limitations

To account for a possible dependency of non-lateralized clinical outcomes, such as NMS, on bilateral active contact locations, we employed linear mixed-models with the within-subject variable ‘hemisphere’.

In contrast, previous studies have focused on effects of unilateral DBS [9, 10, 45] or hemibody motor outcomes [6], or have simplified statistical approaches by ignoring that clinical outcomes depend on bihemispheric DBS [11] and active contact locations are defined by three-dimensional coordinates [6]. Furthermore, previous studies have dichotomized clinical outcomes [11, 37, 46, 47] and neurostimulation locations [8, 48, 49]. Therefore, we preferred the linear mixed-effect models approach as it integrates active contact locations and clinical outcomes as continuous data, i.e. without loss of information due to dichotomization.

Nevertheless, one limitation of our study is the simplified approach to account for the variance in patients’ individual anatomy. The standardization to the Mai-atlas according to the method of Videen et al. corrects differences of patients’ individual anatomy with an accuracy <1 mm [22]. Considering the small differences of mean active contact locations in “responder”/”non-responder” analyses, future studies are required to confirm the preliminary results of this study by employing more sophisticated imaging methods, such as diffusion-tensor imaging. Furthermore, an approach based on active contact locations is limited by the fact that stimulation parameters were not considered although they are likely to influence clinical outcomes. Future studies will need to address these issues.

Although the cohort size of our study (n=50) is one of the biggest in studies of its kind, it did not allow employing clustering and more complex models of active contact locations. More sophisticated statistical analyses in larger cohort sizes are needed to distinguish between the direct effects of neurostimulation on NMS and indirect effects mediated by other NMS, in particular, when considering possible bidirectional interdependencies of NMS (e.g., sleep

improvements may result in mood improvements and vice versa). Furthermore, one also has to acknowledge the importance of clinical practice as STN targeting and DBS programming were, as per clinical routine, guided by optimal motor effects while avoiding adverse effects. Closely connected to this point, motor symptoms and LEDD reduction may be possible confounding factors which could influence NMS, although we have found no significant correlations between the change scores of these parameters. Furthermore, a confounding effect also seems unlikely because of the observation of opposing gradients of LEDD (bigger reduction in more lateral neurostimulation locations) and of non-motor and QoL outcomes (bigger improvement in more medial, anterior, and ventral location of active contacts) which suggests that the observations for LEDD and above mentioned clinical outcomes were not mediated by the same effect.

Due to these methodological limitations, the results of our study are preliminary and one cannot advise changes of clinical procedures on their basis. The advantage of the methods we have used, however, is that they are easily accessible and reproducible by most DBS centers. As new technology, such as directional DBS, enables clinicians to focus neurostimulation on specific STN subregions [24, 50], further studies are needed to investigate the clinical relevance of directing neurostimulation towards non-motor STN subregions.In this context, also a careful monitoring of clinical parameters, such as medication requirements, and possible behavioral adverse effects are key parameters to be taken into consideration when evaluating DBS targeting of STN subregions.

4.4. Conclusion

Our study supports the concept that DBS outcomes depend on active contact locations. The results presented here offer preliminary evidence that DBS in more anterior, medial, and ventral STN regions is beneficial for non-motor outcomes, such as anxiety, depression, sleep,

gastrointestinal symptoms, and overall NMS burden, without negative effects on motor examination and complications in patients with PD. Future studies are required employing more sophisticated methods, such as diffusion-tensor imaging and volume of tissue activated, to integrate patients’ individual neuroanatomy and stimulation parameters. The long-term aim of these analyses is a better knowledge of effects of the location of neurostimulation on clinical outcomes.

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***Figure 1*- Stimulation leads of all patients**

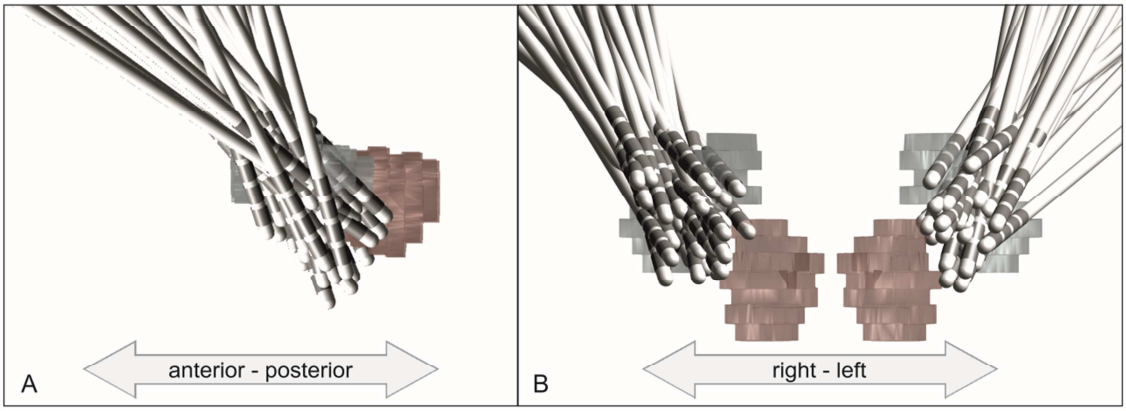

Figure 1 illustrates bilateral stimulation leads of all patients in sagittal (A) and axial (B) planes. Stimulation leads are projected on a three-dimensional version of the Mai-atlas containing the subthalamic nucleus (grey) and the red nucleus (copper) as published previously by Dembek et al., 2017. As this illustration is based on a three dimensional model of the Mai-atlas, non-overlapping projections of the STN and stimulation leads do not exclude an actual neuroanatomical overlap.

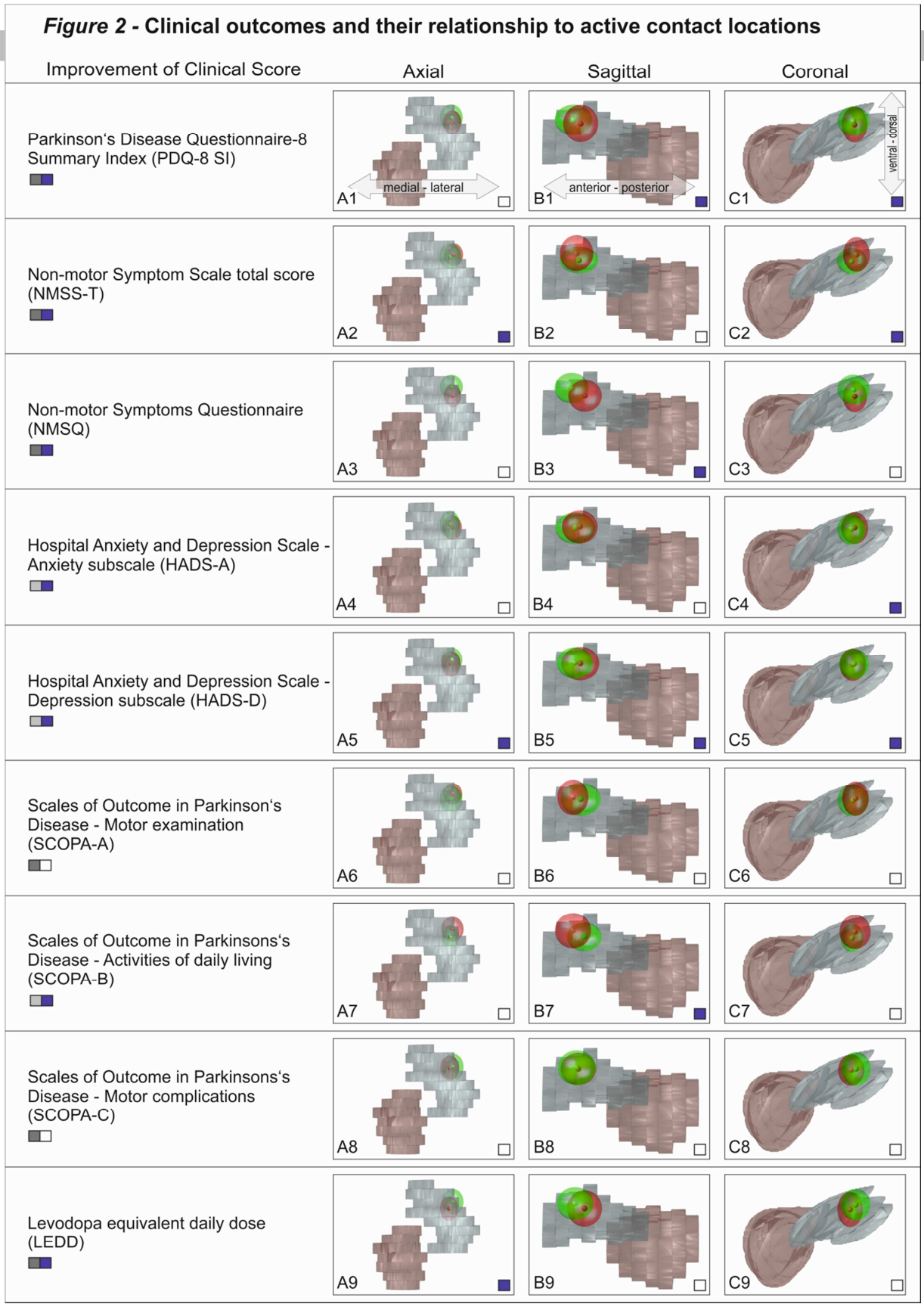

Figure 2 shows the subthalamic nucleus (grey) and red nucleus (copper) in axial (A1-9), sagittal (B1-9), and coronal (C1-9) planes in a three-dimensional model of the Mai-atlas. Green dots illustrate mean locations of active contacts of "responders", i.e. patients who experienced a clinically relevant improvement on respective test scores according to a designated cohort-based threshold improvement (> ½ SD of $Test_{baseline}$). Red dots reflect mean locations of active contacts of patients with stable or worsened test score changes

("non-responders"). The transparent green and red areas surrounding respective dots reflect 1 standard deviation of location of active contacts in respective axis. Dark grey squares highlight significant clinical improvements of respective test scores from baseline to follow-up (after Bonferroni-correction). Light grey squares were used for test scores that showed a trend before Bonferroni-correction. Blue squares illustrate significant result of linear mixed-effect models with Cartesian coordinates for x-, y-, and z-coordinates of active contacts as independent, right and left hemisphere as within-subject, and test changes scores as dependent variables. Fixed effects included coordinates of all three axes. Significant results for x-axis are shown on the axial plane, for y-axis coordinates on the sagittal plane, and for z-axis coordinates on the coronal plane. One slice in this three-dimensional model of the Mai-atlas equals 1.3 mm.

Highlights

- Role of DBS active contact locations on outcomes analyzed with linear mixed models
- These models account for non-lateralized (non-motor) outcomes in bihemispheric DBS
- More anterior, medial, and ventral STN-DBS is related to better non-motor outcomes

Table 1 – Clinical outcomes at baseline and follow-up

Score	n	Baseline		Follow-up		Relative change [%]	Responder rate [%] [a]	Effect size [τ]	p
		mean	SD	mean	SD				
PDQ-8 SI *	48	34.7	16.1	24.9	15.9	-28.2	52.0	0.61	**0.008**
NMSS-T *	47	62.0	34.7	41.5	24.4	-33.1	48.9	0.59	**0.008**
NMSQ *	48	10.5	4.9	7.8	3.8	-26.2	50.0	0.55	**0.008**
HADS-T [‡]	45	10.7	6.6	8.5	5.2	-20.6	33.3	0.33	0.160
SCOPA-A *	49	11.5	6.0	7.6	4.6	-33.9	51.0	1.15	**<0.001**
SCOPA-B [‡]	46	7.0	3.4	5.6	3.2	-20.0	45.7	0.41	0.096
SCOPA-C *	45	4.8	2.9	2.6	2.6	-47.1	51.1	0.76	**<0.001**
LEDD *	49	1135.9	542.1	547.4	271.8	-51.8	69.4	1.09	**<0.001**

Abbreviations: PDQ-8 SI = Parkinson's Disease Questionnaire-8 items Summary Index; **NMSS-T** = Non-motor Symptom Scale total score; **NMSQ** = Non-motor Symptoms Questionnaire; **HADS-T** = Hospital Anxiety and Depression Scale total score; **SCOPA-A, -B, and -C** = Short Outcomes of Parkinson's Disease-motor examination, -activities of daily living, and -motor complications; **HADS-T** = Hospital Anxiety and Depression Scale total score; **LEDD** = levodopa equivalent daily dose.

[a] Percentage of patients who experienced clinically improvement (> ½ SD $Test_{baseline}$)

[τ] Effect sizes were "small" (0.20-0.49) for HADS-T and SCOPA-B, "moderate" (0.5-0.79) for PDQ-8 SI, NMSS-T, NMSQ, and SCOPA-C, and "large" (>0.80) for SCOPA-A and LEDD.

***** Significant improvement at follow-up

[‡] Not significant after Bonferroni-correction, trend before Bonferroni-correction (HADS-T: uncorrected p=0.020, SCOPA-B: uncorrected p=0.014

***Table 2* – Cartesian coordinates of ventral and active DBS contacts**

Axis	Ventral contact [mm]				Active contact [mm]			
	hemisphere				hemisphere			
	left		right		left		right	
	mean	SD	mean	SD	mean	SD	mean	SD
X	-10.45	1.39	10.89	1.82	-11.90	1.35	12.39	1.65
Y	-3.19	1.86	-3.25	2.08	-0.51	1.88	-0.47	1.93
Z	-6.68	2.47	-6.99	2.45	-2.95	1.76	-3.14	1.73

Cartesian coordinates of geometric centers of contacts were identified based on fused preoperative MRI/postoperative CT images (Optivise software). Coordinates were referenced to the mid-commissural point and standardized to the Mai-Atlas. In cases with two or more active contacts the geometric center was calculated.

***Table 3* – Linear mixed-effects model for $Test_{change\ score}$ response based on Cartesian coordinates**

Model [a]	Intercept			X-axis			Y-axis			Z-axis			Significant improvement direction
	β	$F_{(df)}$	p	β	$F_{(df)}$	p	β	$F_{(df)}$	p	β	$F_{(df)}$	p	
PDQ-8 SI *	18.26	$1.51_{(1,92)}$	0.222	-1.21	$1.03_{(1,89)}$	0.311	3.40	$8.48_{(1,94)}$	**0.004**	-2.51	$4.18_{(1,93)}$	**0.044**	medial, anterior
NMSS-T *	71.89	$5.50_{(1,93)}$	**0.021**	-5.59	$5.02_{(1,92)}$	**0.028**	4.17	$2.92_{(1,94)}$	0.091	-6.12	$5.48_{(1,93)}$	**0.021**	medial, ventral
NMSQ *	4.04	$0.92_{(1,95)}$	0.339	0.00	$0.00_{(1,94)}$	0.994	0.69	$4.45_{(1,96)}$	**0.037**	0.28	$0.62_{(1,95)}$	0.432	anterior
HADS-A *	3.36	$1.26_{(1,89)}$	0.265	-0.28	$1.31_{(1,88)}$	0.255	0.44	$3.74_{(1,90)}$	0.056	-0.55	$4.72_{(1,90)}$	**0.032**	ventral
HADS-D *	6.27	$4.37_{(1,89)}$	**0.039**	-0.55	$5.06_{(1,87)}$	**0.027**	0.61	$7.23_{(1,90)}$	**0.009**	-0.51	$4.10_{(1,90)}$	**0.046**	medial, anterior, ventral
SCOPA-A	5.22	$1.46_{(1,97)}$	0.231	-0.16	$0.22_{(1,96)}$	0.637	-0.28	$0.67_{(1,98)}$	0.417	-0.18	$0.27_{(1,98)}$	0.608	
SCOPA-B *	3.00	$1.00_{(1,92)}$	0.321	-0.21	$0.70_{(1,91)}$	0.405	-0.48	$4.51_{(1,92)}$	**0.036**	-0.20	$0.67_{(1,90)}$	0.416	posterior
SCOPA-C	-1.36	$0.29_{(1,89)}$	0.589	0.30	$2.07_{(1,88)}$	0.154	-0.19	$0.96_{(1,90)}$	0.330	0.00	$0.00_{(1,89)}$	0.985	
LEDD *	-223.52	$0.28_{(1,97)}$	0.599	76.02	$5.04_{(1,94)}$	**0.027**	39.66	$1.48_{(1,98)}$	0.227	28.96	$0.69_{(1,98)}$	0.410	lateral

Abbreviations: β = estimated regression coefficient; **df** = degrees of freedom (corrected df were rounded to the nearest integer); **PDQ-8 SI** = Parkinson's Disease Questionnaire-8 items Summary Index; **NMSS-T** = Non-motor Symptom Scale total score; **NMSQ** = Non-motor Symptoms Questionnaire; **SCOPA-A, -B, and -C** = Short Outcomes of Parkinson's Disease-motor examination, -activities of daily living, and -motor complications; **HADS-A and -D** = Hospital Anxiety and Depression Scale -anxiety and -depression subscales; **LEDD** = levodopa equivalent daily dose.

[a] Type 3 tests in the linear mixed-effect models with independent variables: x-, y- and z-coordinates; within-subject parameter: hemisphere (to account for effects of bilateral neurostimulation on outcomes); dependent variable: $Test_{change\ scores}$; fixed effects: x-, y-, and z-axis. Positive β values reflect beneficial clinical outcomes associated with more lateral/anterior/dorsal active contact locations and negative β values with more medial/posterior/ventral locations.

***** Significant responses for respective scales.